Synthesis of Tetrahydropyridoimidazole-2-acetates: Effect of Carboxy and Methoxycarbonyl Groups at C(2) on the Inhibition of Some β- and α-Glycosidases

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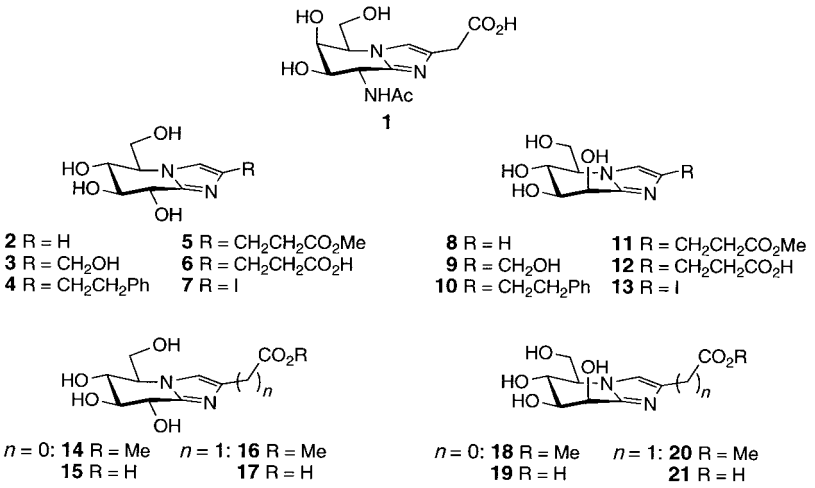
The *gluco*- and *manno*-tetrahydropyridoimidazole-2-acetates and -acetic acids **16** and **17**, and **20** and **21**, respectively, were synthesized by condensation, in the presence of $HgCl_2$, of the known thionolactam **26** with the β-amino ester **25** that was obtained by addition of AcOMe to the imine **22**, followed by debenzylation. The resulting methyl esters **16** and **20** were hydrolyzed to the acetic acids **17** and **21**. The (methoxycarbonyl)-imidazole **14** and the acid **15** were obtained *via* the known aldehyde **29**. The imidazoles **14**–**17**, **20**, and **21** were tested as inhibitors of the β-glucosidase from *Caldocellum saccharolyticum*, the α-glucosidase from brewer's yeast, the β-mannosidase from snail, and the α-mannosidase from *Jack* beans (*Tables 1–3*). There is a similar dependence of the K_i values on the nature of the *C(2)*-substituent in the *gluco*- and *manno*-series. With the exception of **19**, *manno*-imidazoles are weaker inhibitors than the *gluco*-analogues. The methyl acetates **16** and **20** are 3–4 times weaker than the methyl propionates **5** and **11**, in agreement with the hydrophobic effect. The *gluco*-configured (methoxycarbonyl)-imidazole **14** is 20 times weaker than the methyl acetate **16**, reflecting the reduced basicity of **14**, while the *manno*-configured (methoxycarbonyl)-imidazole **18** is only 1.2 times weaker than the methyl acetate **20**, suggesting a binding interaction of the MeOCO group and the β-mannosidase. The carboxylic acids **6**, **12**, **15**, **17**, **19**, and **21** are weaker inhibitors than the esters, with the propionic acids **6** and **12** being the strongest and the carboxy-imidazoles **15** and **19** the weakest inhibitors. The *manno*-acetate **21** inhibits the β-mannosidase *ca.* 8 times less strongly than the propionate **12**, but only 1.5 times more strongly than the carboxylate **19**, suggesting a compensating binding interaction also of the COOH group and the β-mannosidase. The α/β selectivity for the *gluco*-imidazoles ranges between 110 for **15** and $13.4 \cdot 10^3$ for **6**; the *manno*-imidazoles are less selective. The methyl propionates proved the strongest inhibitors of the α-glucosidase (IC_{50} (**5**) = 25 μM) and the α-mannosidase (K_i(**11**) = 0.60 μM).

Introduction. – Nagstatin (**1**), a *N*-acetylgalactosamine-derived tetrahydroimidazopyridine possessing a carboxymethyl substituent at C(2) [1] was isolated from the fermentation broth of *Streptomyces amakusaensis* in 1992 [2] and synthesized in 1995 by *Tatsuta et al.* [3][4]. It inhibits several glycosidases, most notably hog kidney *N*-acetyl-β-D-glucosaminidase (IC_{50} = 4 nM) [2][5]. The carboxymethyl group at C(2) does not appear to be important for the inhibitory activity, since 'debranched' nagstatin analogues and related *C(2)*-unsubstituted glucose- and mannose-derived tetrahydroimidazopyridines are also potent inhibitors of β-glycosidases [5–7]. These observations and the rationalisation of the inhibitory activity of these and analogous azoles – their similarity with the putative reaction intermediate, and the cooperative interaction of the azole ring with the catalytic acid and nucleophile – indicated a negligible role for the substituents at C(2) [8–10]. Subsequently, however, it was shown that *C(2)*-substituents of tetrahydropyridoimidazoles (and corresponding substituents of related azoles and pyrroles) can strongly affect the inhibitory properties, either indirectly, by competing with the catalytic acid for H-bonding to the 'glycosidic' heteroatom, and/or

directly, by interacting in their own right with the glycosidases [11–14]. More recently, we compared the effect of the nature of the *C(2)*-substituents of the *gluco*-configured tetrahydroimidazopyridines **2**–**7** on the inhibition of the β-glucosidases from *Caldocellum saccharolyticum* (family 1) and from sweet almonds to the effect of the same substituents of the *manno*-imidazoles **8**–**13** on the inhibition of the β-mannosidase from snail, arguing that the similar relative effect of these substituents evidences that the reaction coordinates in the vicinity of the reactive intermediates for β-glucosidases of family 1, and the snail β-mannosidase should not differ significantly[1]) [14]. Among the *C(2)*-substituted imidazoles **2**–**13**, the *gluco*-configured methyl propionate **5** and its *manno*-configured analogue **11** were two of the strongest inhibitors of β-glycosidases [12][14]. The carboxylic acids **6**, **12**, and **19** are all weaker inhibitors than the corresponding esters **5**, **11**, and **18**. The *manno*-configured imidazole **18** possessing a MeOCO group at C(2) group is a significantly weaker inhibitor than the methyl propionate **11**. It is not clear how much of this difference is due to the size and shape of the substituents, and how much to the effect on the pK_{HA} value of the imidazoles (pK_{HA} (**11**) = 5.52; pK_{HA} (**18**) < 2.2 [14]). We wished, therefore, to compare the inhibition by the *gluco*-configured methyl esters **14**, **16**, and **5** and of the *manno*-configured analogues **18**, **20**, and **11** to each other, and to the corresponding *gluco*- and *manno*-configured acids **15**, **17**, and **6**, and **19**, **21**, and **12**, respectively, to check for more-subtle differences of these substituents on the inhibition of β-glucosidases and the β-mannosidase. For this, we had to synthesize the methyl acetates **16** and **20** and the corresponding acids **17** and **21**.

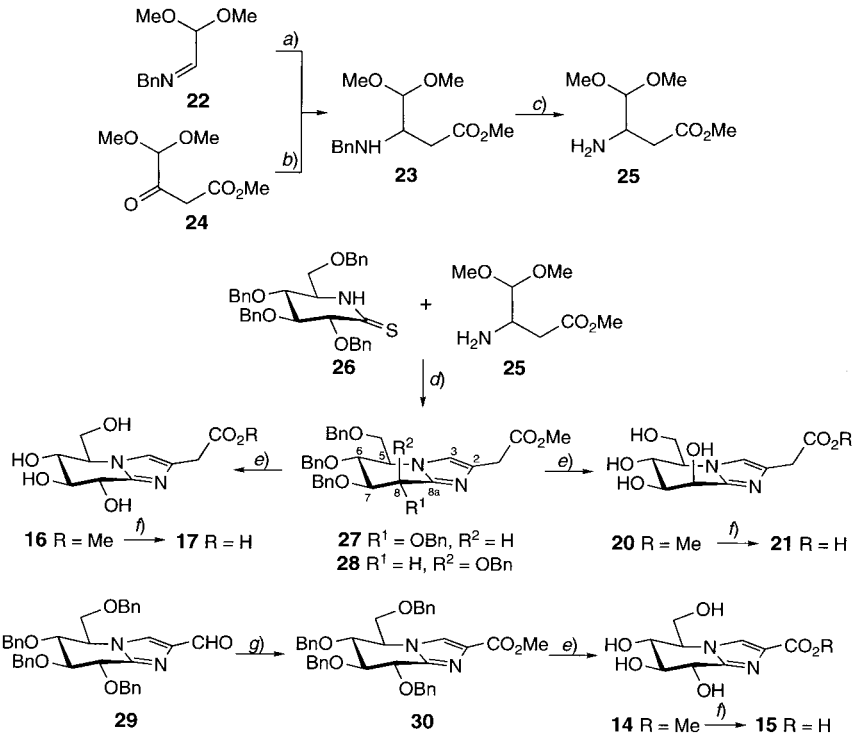


So far, *C(2)*-substituted imidazopyridines were mostly synthesized *via C(2)*-iodoimidazoles [12][14] that are derived in two steps from the 2,3-unsubstituted imidazoles; these were prepared by condensing the thionolactam **26** with 2-aminoacetaldehyde

[1]) Differences between the reaction coordinates preceding the transition state were expected on the basis of the different interaction of the catalytic nucleophile with HO–C(2) in β-glucosidases *vs.* β-mannosidases [15] and evidenced by comparing *gluco* and *manno* isoquinuclidines [16][17].

dimethyl acetal [7]. We planned to obtain **17** and **21** in a shorter, more-convergent way from **26** and the β-amino ester **25** (*Scheme*). For a more-comprehensive structure–activity relationship of C(2)-substituted *gluco*- and *manno*-configured imidazole esters and acids we also required the *gluco*-configured methyl imidazole-2-carboxylate **14** and the corresponding acid **15**.

Scheme 1



a) AcOMe, BuLi, $(i\text{-Pr})_2NH$, $BF_3 \cdot OEt_2$, THF, $-78°$; 63%. *b*) 1. $BnNH_2$, AcOH, CH_2Cl_2; 2. $NaBH(OAc)_3$; 3%. *c*) H_2, Pd/C, MeOH; 64%. *d*) 1. $HgCl_2$, THF; 2. $TsOH \cdot H_2O$, toluene, 60°; 81% of **27**/**28** 56:44. *e*) H_2, Pd/C, AcOEt/MeOH/AcOH; 91% of **16**; 87% of **20**; 95% of **14**. *f*) KOH, $EtOH/H_2O$, 50°; 86% of **17**; 81% of **21**; 80% of **15**. *g*) MnO_2, NaCN, AcOH/MeOH; 77%.

Synthesis. – We planned to synthesize the *gluco*- and *manno*-configured methyl esters **16** and **20** by condensing the gluconothio-1,5-lactam **26** [7] with the β-amino ester **25**. While the synthesis of imidazoles by condensation of thionolactams with 2-aminoacetaldehyde dimethyl acetal is well-precedented [7][18–20], there are only very few examples of the condensation with substituted amino acetals [21][22]. To prepare the methyl ester **25**[2]) (*Scheme*), we started from benzyl[(2,2-dimethoxy)-ethylidene]amine (**22**), which we recently described as useful precursor of α-amino-

[2]) The *tert*-butyl ester analogues of (*S*)-, (*R*)-, and (*RS*)-**25** were synthesized in four steps and in overall yields of 52–68% from commercially available Z-Asp(O^{t}Bu)-H [23].

phosphonates [22]. Treatment of **22** with the *in situ* generated lithium enolate of methyl acetate[3]) in the presence of $BF_3 \cdot OEt_2$ gave the benzylamine **23**[4]) (63%); **22** did not react in the absence of $BF_3 \cdot OEt_2$. The synthesis of **23** by reductive amination of the β-keto ester **24** [42] with $BnNH_2$ (AcOH, $NaBH(OAc)_3$ [43–45]) was not promising; **23** was isolated in only 3% from the complex crude product. The β-amino ester **25** was obtained by hydrogenolysis (10% Pd/C) of **23** and isolated in 64% yield by bulb-to-bulb distillation under reduced pressure.

In contradistinction to the condensation of 2-aminoacetaldehyde dimethyl acetal with the thionolactam **26** [7], the one of the substituted amino acetal **25** required a catalyst. Condensation of **25** with **26** in the presence of $HgCl_2$, followed by treatment of the crude with $TsOH \cdot H_2O$ provided 57% (25-mg scale) of a 58:42 mixture of the *gluco*-imidazole **27** and the *manno*-isomer **28**. Lower yields (22–52%) of **27**/**28** resulted by replacing $HgCl_2$ by HgO, $HgBr_2$, $HgCl_2/Et_3N$, $Hg(OAc)_2$, or $Hg(OTf)_2$. The ratio **27**/**28** varied between 68:32 (HgO) and 45:55 ($Hg(OTf)_2$) (*cf. Exper. Part*). The yield of **27** and **28** increased to 81% (**27**/**28** 56:44) by conducting the reaction on a larger scale (235 mg of **26**) in the presence of $HgCl_2$. The resulting imidazoles were readily separated by chromatography to give **27** (44%), **27**/**28** 50:50 (2%), and **28** (35%). Hydrogenolysis (10% Pd/C, AcOH) of **27** and **28** provided the *gluco*- and *manno*-esters **16** and **20**, respectively, which were hydrolyzed with 0.4M KOH in EtOH/H_2O at 50° to the corresponding *C(2)*-carboxymethyl substituted imidazoles **17** (86%) and **21** (81%). This synthesis afforded **17** and **21** in four steps from **26**, and in overall yields of 35 and 25%, respectively.

The *gluco*-configured methoxycarbonyl- and carboxy-imidazoles **14** and **15** were prepared similarly to the *manno*-analogues [14]. Oxidation of the aldehyde **29** [12] with MnO_2 in the presence of NaCN and MeOH [46] provided the methyl ester **30** (77%) that was debenzylated (H_2, 10% Pd/C, AcOH) to the tetrol **14** (95%; 73% from **29**). Hydrolysis (KOH in EtOH/H_2O, 50°) yielded 80% of the carboxy-imidazole **15** (59% from **29**).

In agreement with previous observations [7][11][12][14], the *C(2)*-substituents do not affect the solution conformation of the tetrahydroimidazopyridines. Thus, the benzylated *gluco*- and *manno*-imidazoles **27**, **28**, and **30** are 2:1 mixtures of the $^7H_6$ and the $^6H_7$ conformers[5]), while the unprotected imidazoles **14**–**17**, **20**, and **21** adopt a $^7H_6$ conformation (see *Tables 4* and *6* in *Exper. Part*). The ^{13}C signals of C(5)–C(8) of **27** and **28** (*Table 5* in *Exper. Part*) were assigned on the basis of HSQC.GRASP spectrum; those of the other imidazoles were assigned by analogy. The formation of the [(methoxycarbonyl)methyl]-imidazoles **27** and **28** from **26** is confirmed by the disappearance of the NH signal, by ^{13}C *s*'s at 134.70 ppm (**27** and **28**), ^{13}C *d*'s at 115.28 (**27**) and 117.18 ppm (**28**), and strong IR C=O bands at 1737 and 1738 cm^{-1} for **27** and **28**, respectively. The assignment of the *gluco*- and *manno*-configuration to **27**

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[3]) The addition of enolates of methyl acetate to imines [24][25], *N*-sulfinyl imines [26–39], and *N*-acylpyrazolines [40] are well-documented.

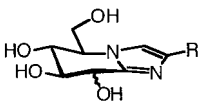
[4]) (*R*)-**23** was prepared from 5-[(*R*)-menthyloxy]-furan-2(5*H*)-one in two steps in an overall yield of 45% and used for the synthesis of β-lactams [41]. No spectroscopic data of (*R*)-**23** were reported.

[5]) The direction of numbering of imidazopyridines (*cf.* **27** in *Scheme*) is opposite to that of pyranosides. Thus, the sides above and below the plane of the imidazoles, as defined by the clockwise and counterclockwise numbering, are interchanged relative to those defined by carbohydrate nomenclature.

and **28**, respectively, is based on the value of $J(7,8)$ (5.3 and 3.1 Hz, resp.; *cf. Scheme*). The formation of the methoxycarbonyl-imidazole **30** is confirmed by the disappearance of the CHO signal in the ^{1}H-NMR spectrum, by the ^{1}H *s* at 3.92 ppm (MeO), the ^{13}C *s* at 163.17 ppm, and a strong IR C=O band at 1716 cm^{-1}.

Enzymatic Tests and Discussion. – The *gluco*- and *manno*-imidazopyridines **14**–**17**, **20**, and **21** were tested as inhibitors of the β-glucosidase from *Caldocellum saccharolyticum* (phosphate buffer, pH 6.8, 55°), α-glucosidase from brewer's yeast (phosphate buffer, pH 6.8, 37°), β-mannosidase from snail (acetate buffer, pH 4.5, 25°), and α-mannosidase from *Jack* beans (acetate buffer + $ZnCl_2$, pH 4.5, 37°), using the corresponding 4-nitrophenyl glycopyranosides as substrates. The data for the inhibition of the β-glucosidase and β-mannosidase are summarized in *Table 1*, and compared to the inhibition of these enzymes by the known *gluco*-imidazoles **5** and **6**, and the *manno*-imidazoles **11**, **12**, **18**, and **19**. The data for the inhibition of the α-glucosidase, and the selectivity of the inhibition of β- and α-glucosidases by *gluco*-imidazoles are compiled in *Table 2*. The data for the inhibition of the α-mannosidase, and the selectivity of the inhibition of the β- and α-mannosidases by *manno*-imidazoles are listed in *Table 3*.

Table 1. pK_{HA} *Values of the C(2)-Substituted* gluco- *and* manno-*Imidazoles* **5**, **6**, **11**, **12**, *and* **14**–**21**, *and Comparison of Their Inhibition of the* β*-Glucosidase from* Caldocellum saccharolyticum *and of the* β*-Mannosidase from Snail*

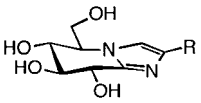


	gluco-Imidazoles		Inhibition of β-glucosidase[a])		*manno*-Imidazoles		Inhibition of β-mannosidase[b])		Comparison of K_i values	
R	No.	pK_{HA}	K_i [nM]		No.	pK_{HA}	K_i [nM]		K_i (rel.)	
									β-glucosidase	β-mannosidase
Esters										
COOMe	**14**	[c])	103	(α = 3.4)	**18**[d])	–	142	(α = 4.3)	57.2	5.1
CH_2COOMe	**16**	5.03	5.0[e])		**20**	4.61	117	(α = 3.4)	2.8	4.2
CH_2CH_2COOMe	**5**[f])	6.17	1.8	(α = 2.5)	**11**[d])	5.52	28		≡1	≡1
Acids										
COOH	**15**	4.95[g])	2660	(α = 2.7)	**19**[d])	4.70	1210	(α = 4.8)	295.6	12.1
CH_2COOH	**17**	6.40[g])	95	(α = 1.6)	**21**	5.08[g])	810		10.6	8.1
CH_2CH_2COOH	**6**[f])	4.06/7.05	9.0[h])		**12**[d])	4.15	100	(α = 5.3)	≡1	≡1

[a]) At 55° and pH 6.8. [b]) At 25° and pH 4.5. [c]) No inflection of the titration curve was observed between pH values of 2.2 and 6.0. [d]) Data taken from [14]. [e]) Non-competitive inhibition. [f]) Data taken from [12]. [g]) No additional pK_{HA} value was observed between pH values 2.2–5.5 (**15**), 2.9–7.9 (**17**), 2.6–5.4 (**21**). [h]) IC_{50}/2.

The data in *Table 1* show qualitatively the same dependence of the K_i values on the nature of the *C(2)*-substituent in the *gluco*- and *manno*-series. With the exception of **19**, the *manno*-imidazoles are weaker inhibitors than the corresponding *gluco*-imidazoles. Considering the different pH optima of the β-glycosidases and the different extent to which the imidazoles are protonated at the pH of the assay, the quantitative differences between the relative K_i values for the *gluco*- and *manno*-imidazoles are small. On the

Table 2. *p*K_{HA} *Values of the* C(2)*-Substituted* gluco*-Imidazoles* **5**, **6**, *and* **14**–**17**, *and Comparison of Their Inhibition of the* α*-Glucosidase from Brewer's Yeast and of the* β*-Glucosidase from* Caldocellum saccharolyticum



R	*gluco*-Imidazoles No.	pK_{HA}	Inhibition of α-glucosidase[a]) IC_{50} [μM]	Inhibition of β-glucosidase[b]) K_i [nM]	Comparison of K_i values[c]) K_i (rel) α-glucosidase	K_i (α-glucosidase)/ K_i (β-glucosidase)
Esters						
COOMe	**14**	[d])	489	103	19.6	$2.37 \cdot 10^3$
CH_2COOMe	**16**	5.03	69	5.0	2.8	$6.90 \cdot 10^3$
CH_2CH_2COOMe	**5**[e])	6.17	25	1.8	≡1	$6.94 \cdot 10^3$
Acids						
COOH	**15**	4.95[f])	598	2660	2.5	$0.11 \cdot 10^3$
CH_2COOH	**17**	6.40[f])	125	95	0.5	$0.66 \cdot 10^3$
CH_2CH_2COOH	**6**[e])	4.06/7.05	242	9.0	≡1	$13.44 \cdot 10^3$

[a]) At 37° and pH 6.8. [b]) At 55° and pH 6.8; only K_i values shown (for the inhibition type see *Table 1*). [c]) K_i Values for the α-glucosidase were calculated as $IC_{50}/2$. [d]) No inflection of the titration curve was observed between pH values of 2.2 and 6.0. [e]) Data taken from [12]. [f]) No additional pK_{HA} value was observed between pH values 2.2–5.5 (**15**) and 2.9–7.9 (**17**).

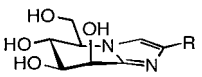
basis of this observation, there should not be a significant difference between the reaction coordinates, in the vicinity of the reactive intermediates, for β-glucosidases of family 1 and snail β-mannosidase [14].

The methyl propionates **5** and **11** are the strongest inhibitors of the β-glycosidases. Weakest are the methyl carboxylates **14** and **18**. The methyl acetates **16** and **20** inhibit the β-glucosidase and the β-mannosidase 3–4 times less strongly than the corresponding methyl propionates **5** and **11**. This difference corresponds to the increase of hydrophobic surface area, amounting to a minimum of 0.68 kcal mol^{-1} or a 3.2-fold increase in binding constant for a Me and similarly for a CH_2 group[6]). The *gluco*-configured methoxycarbonyl-imidazole **14** is a 20 times weaker inhibitor of the β-glucosidase than the methyl acetate **16**. This difference is larger than expected from the hydrophobic effect, and reflects the reduced basicity of the methoxycarbonyl-imidazole **14** ($pK_{HA} < 2.2$; see *Table 1*) and the weaker interaction with the catalytic acid. The corresponding *manno*-configured methoxycarbonyl-imidazole **18** is, however, only a 1.2-times weaker inhibitor of the β-mannosidase than the methyl acetate **20**. As the pK_{HA} value of **18** is close to that of **14** [14], one has to postulate a compensating interaction of the MeOCO substituent with the β-mannosidase.

The *gluco*- and *manno*-configured carboxylic acids **6**, **12**, **15**, **17**, **19**, and **21** proved, overall, weaker inhibitors of the β-glycosidases than the corresponding esters. One finds a similar dependence of the inhibition of the β-glycosidases on the size of the

6) The contribution of hydrophobic interactions in the binding of biologically active compounds to their receptors has been reviewed by *Davis* and *Teague* [47]. Recent examples of this effect on the inhibitory activity of β-glycosidases include imidazopyridines of type **2** [12][14][48], D-gluconolactam oximes [49], β-D-glucosylamines [50], D-gluconamidines [51][52], and 2,5-dideoxy-2,5-imino-D-mannitols [53–55].

Table 3. *p*K$_{HA}$ *Values of the* C(2)-*Substituted* manno-*Imidazoles* **11**, **12**, *and* **18**–**21**, *and Comparison of Their Inhibition of the* α-*Mannosidase from* Jack *Beans and of the* β-*Mannosidase from Snail*



	manno-Imidazoles		Inhibition of α-mannosidase[a])	Inhibition of β-mannosidase[b])	Comparison of K_i values	
R	No.	pK_{HA}	K_i [μM]	K_i [nM]	K_i (rel) α-mannosidase	K_i (α-mannosidase)/ K_i (β-mannosidase)
Esters						
COOMe	**18**[c])	–	12.5	142	20.8	88.0
CH_2COOMe	**20**	4.61	0.91	117	1.5	7.8
CH_2CH_2COOMe	**11**[c])	5.52	0.60	28	≡1	21.4
Acids						
COOH	**19**[c])	4.70	1.33	1210	1.7	1.1
CH_2COOH	**21**	5.08[d])	1.85	810	2.4	2.3
CH_2CH_2COOH	**12**[c])	4.15	0.78	100	≡1	7.8

[a]) At 37° and pH 4.5; competitive inhibition for all imidazoles. [b]) At 25° and pH 4.5; only K_i values shown (for the inhibition type, see *Table 1*). [c]) Data taken from [14]. [d]) No additional pK_{HA} value was observed between pH values of 2.6 and 5.4.

substituent at C(2) as for the ester analogues; the propionic acids **6** and **12** are the strongest inhibitors and the imidazole-carboxylic acids **15** and **19** the weakest ones. The *gluco*-configured carboxymethyl-imidazole **17** is a 10 times weaker inhibitor of the β-glucosidase than **6**, and a 28 times stronger inhibitor than **15**. In both cases, the differences are larger than expected from the difference of hydrophobicity of the substituents at C(2). The pK_{HA} values of **6**, **15**, and **17** (see *Table 1*), and the pH value (6.8) of the enzymatic assay suggest that the *gluco*-configured carboxylic acids are, at least in part, bound as zwitterions. The lower inhibitory activity of the acids (as compared to the esters) may reflect the impaired interaction of the partially protonated imidazoles with the catalytic acid. The weak inhibition of the β-glucosidase by **15** may be due to the reduced basicity of this imidazole (see *Table 1*). A disruptive interaction of the glycosidases with the (solvated?) carboxylate anion cannot be excluded.

In agreement with the inhibition of the β-glucosidases by the propionate **6** and acetate **17**, respectively, the *manno*-configured acetate **21** inhibits the β-mannosidase *ca.* 8 times less strongly than the propionate **12**. However, **21** is only a 1.5-times stronger inhibitor than the carboxylate **19**. The pH value (4.5) of the enzymatic assay of the β-mannosidase and the pK_{HA} values of the imidazoles **12**, **19**, and **21** (see *Table 1*) suggest that the inhibitors are bound as imidazolium salts **12**·H$^+$, **19**·H$^+$, and **21**·H$^+$. The remarkably strong inhibition of the β-mannosidase by the carboxylic acid **19** supports a binding interaction between the COOH group of **19** and the enzyme, similarly as suggested above for the MeOCO group of **18**.

Tables 2 and *3* show the data for the inhibition of the α-glucosidase from brewer's yeast (IC_{50} values) and the α-mannosidase from *Jack* beans (K_i values). There is no clear correlation between the α/β selectivity and the strength of the inhibition of β-glycosidases. The selectivity for the inhibition of the α- *vs.* β-glucosidases by *gluco*-imidazoles ranges between 110 for the carboxylate **15** and $13.4 \cdot 10^3$ for the propionic acid **6**. The *manno*-imidazoles are less selective with the selectivity for the inhibition of

the α- *vs.* β-mannosidases varying between 1.1 for the carboxylate **19** and 88 for the methyl carboxylate **18**. The *gluco*- and *manno*-configured methyl propionates **5** and **11** proved the strongest inhibitors of the α-glucosidase ($IC_{50} = 25$ μM) and the α-mannosidase ($K_i = 0.60$ μM), respectively.

We thank *M. Schneider* for the pK_{HA} determinations, Dr. *B. Bernet* for checking the *Exper. Part*, and the *Swiss National Science Foundation* and *Oxford Glycosciences Ltd.*, Abingdon (UK), for generous support.

Experimental Part

General. Solvents were distilled: THF from Na and benzophenone, CH_2Cl_2 from P_2O_5, MeOH, $(i\text{-}Pr)_2NH$, and $BnNH_2$ from CaH_2, and AcOMe from $MgSO_4$. Reactions were carried out under Ar, unless stated otherwise. Qual. TLC: precoated silica-gel plates (*Merck* silica gel *60 F_{254}*); detection by heating with 'mostain' (400 ml of 10% H_2SO_4 soln., 20 g of $(NH_4)_6\,Mo_7O_{24}\cdot 6\,H_2O$, 0.4 g of $Ce(SO_4)_2$). Flash chromatography (FC): silica gel *Fluka 60* (0.04–0.063 mm). Optical rotations: 1-dm cell at 25°, 589 nm. UV Spectra (*ca.* 0.2 mM solns.) were taken in 1-cm cell at 25° in the range of 190 to 500 nm (log ε values in parentheses). FT-IR spectra: KBr or *ca.* 2% soln. in $CHCl_3$, absorption in cm^{-1}. ^1H- and ^{13}C-NMR spectra: chemical shifts δ in ppm rel. to TMS as external standard, and coupling constants J in Hz. HR-MALDI-MS: in gentisic acid (=2,5-dihydroxybenzoic acid, DHB) matrix. The pK_{HA} values were determined in H_2O by potentiometric titration with HCl at 25°. The β-glucosidase from *Caldocellum saccharolyticum* (EC 3.2.1.21, as a lyophilized powder, *Sigma G-6906*), α-glucosidase from brewer's yeast (maltase, EC 3.2.1.20, as a lyophilized powder, *Fluka 63412*), β-mannosidase from snail acetone powder (EC 3.2.1.25, as a suspension in 3.0M $(NH_4)_2SO_4$ containing 10 mM AcONa, pH *ca.* 4.0, *Sigma M-9400*), α-mannosidase from *Jack* beans (EC 3.2.1.24, as a suspension in 3.0M $(NH_4)_2SO_4$ and 0.1 mM zinc acetate, pH *ca.* 7.5, *Sigma M-7257*), 4-nitrophenyl β-D-glucopyranoside (*Fluka 73676*), 4-nitrophenyl α-D-glucopyranoside (*Fluka 73673*), 4-nitrophenyl β-D-mannopyranoside (*Sigma N-1268*), and 4-nitrophenyl α-D-mannopyranoside (*Sigma N-2127*) were used without further purification.

Methyl 3-(Benzylamino)-4,4-dimethoxybutanoate (**23**). *a*) At −78°, a soln. of **22** (6.80 g, 35.2 mmol) in THF (15 ml) was treated with $BF_3\cdot OEt_2$ (4.80 ml, 39.0 mmol) and stirred for 1 h. In the meantime, a soln. of LDA (prepared by addition of BuLi (1.6M, 44.5 ml, 71.2 mmol) to a soln. of $(i\text{-}Pr)_2NH$ (11.0 ml, 77.8 mmol) in THF (50 ml) at −78°) was treated with freshly distilled AcOMe (11.8 ml, 0.148 mol), stirred for 35 min at −78°, and treated with the THF soln. of **22** and $BF_3\cdot OEt_2$. The mixture was stirred for 150 min at −78°, treated with H_2O (50 ml), stirred for 15 min at 22°, and diluted with Et_2O (250 ml). After separation, the org. layer was washed with H_2O (100 ml), and the aq. layer was extracted with Et_2O (2 × 80 ml). The combined org. layers were washed with brine (250 ml), dried ($MgSO_4$), filtered, and evaporated. FC (hexane/AcOEt 3:1 → 2:1 → 1:1) gave **22** (1.47 g, 22%) and **23** (5.94 g, 63%).

b) At 22°, a soln. of **24** (540 mg, 3.07 mmol) in CH_2Cl_2 (30 ml) was successively treated with $BnNH_2$ (0.38 ml, 3.48 mmol) and AcOH (0.19 ml, 3.32 mmol), stirred for 5 min, and treated with $NaBH(OAc)_3$ (975 mg, 4.60 mmol). The mixture was stirred for 16 h at 22°, treated with sat. $NaHCO_3$ soln. (40 ml), diluted with CH_2Cl_2 (50 ml), and washed with sat. $NaHCO_3$ soln. (2 × 50 ml). The combined aq. layers were extracted with CH_2Cl_2 (2 × 50 ml). The combined org. layers were washed with H_2O (60 ml) and brine (60 ml), dried ($MgSO_4$), filtered, and evaporated. The ^1H-NMR spectrum of the crude (816 mg) showed a complex mixture of products from which **23** (22 mg, 3%) was isolated by FC (hexane/AcOEt 2:1 → 1:1).

Data of **23**: Colourless oil. R_f (hexane/AcOEt 1:1) 0.46. IR ($CHCl_3$): 3337*w*, 3029*m*, 3011*m*, 2954*m*, 2837*m*, 1951*w*, 1877*w*, 1810*w*, 1731*s*, 1604*w*, 1495*w*, 1454*m*, 1439*m*, 1362*m*, 1285*m*, 1259*m*, 1167*m*, 1132*s*, 1115*s*, 1075*s*, 1029*m*, 1011*m*, 968*m*, 913*m*. ^1H-NMR ($CDCl_3$, 300 MHz): 1.72–1.82 (br. *s*, exchange with CD_3OD, NH); 2.46 (*dd*, $J = 6.5$, 15.3, H−C(2)); 2.59 (*dd*, $J = 5.6$, 15.3, H′−C(2)); 3.18–3.27 (*m*, H−C(3)); 3.35, 3.40 (2*s*, $(MeO)_2C(4)$); 3.66 (*s*, CO_2Me); 3.78, 3.87 (2*d*, $J = 13.1$, PhCH_2); 4.31 (*d*, $J = 5.0$, H−C(4)); 7.18–7.44 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 34.94 (*t*, C(2)); 51.49 (*q*, CO_2Me); 51.51 (*t*, PhCH_2); 54.87, 55.67 (2*q*, $(MeO)_2C(4)$); 55.85 (*d*, C(3)); 106.18 (*d*, C(4)); 126.75 (*d*, C(4) of Ph); 127.97 (*d*, C(2) and C(6) of Ph); 128.15 (*d*, C(3) and C(5) of Ph); 140.16 (*s*, C(1) of Ph); 172.62 (*s*, C(1)). EI-MS: 267 (<1, M^+), 236 (5, $[M - MeO]^+$), 204 (<1, $[M - MeO - MeOH]^+$), 192 (60, $[M - (MeO)_2CH]^+$), 91 (100, $C_7H_7^+$), 75 (17, $(MeO)_2CH^+$), 65 (6), 28 (5). HR-ESI-MS: 1067.3520 (8), 1051.4210 (13), 957.3619 (27), 696.2766 (100), 529.2487 (21), 268.1550 (56, $[M + H]^+$, $C_{14}H_{22}NO_4^+$; calc. 268.1549). Anal. calc. for $C_{14}H_{21}NO_4$ (267.32): C 62.90, H 7.92, N 5.24; found: C 63.02, H 7.90, N 5.07.

Methyl 3-Amino-4,4-dimethoxybutanoate (**25**). *a*) A suspension of **23** (710 mg, 2.66 mmol) and 10% Pd/C (350 mg) in MeOH (17 ml) was hydrogenated at the atmospheric pressure and 22° for 5 h and filtered over *Celite*. Evaporation and bulb-to-bulb distillation (110°/0.5 Torr) of the yellowish oil gave **25** (302 mg, 64%).

b) A suspension of **23** (4.10 g, 15.3 mmol) and 10% Pd/C (410 mg) in MeOH (100 ml) was hydrogenated at 6 bar and 22° for 1 h and filtered over *Celite*. Evaporation (→ yellowish oil) and distillation (micro-distillation apparatus; 110°/0.5 Torr) gave **25** (1.54 g, 57%).

Data of **25**: Colourless liquid. R_f (AcOEt/MeOH 10:1) 0.10. B.p. 80°/0.5 Torr. IR ($CHCl_3$): 3387*w*, 3320*w*, 3028*m*, 2997*m*, 2955*s*, 2836*m*, 1731*s*, 1583*m*, 1439*s*, 1414*w*, 1371*m*, 1327*m*, 1297*m*, 1263*m*, 1168*s*, 1121*s*, 1072*s*, 1018*m*, 975*m*, 916*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.42–1.56 (br. *s*, exchange with CD_3OD, NH_2); 2.30 (*dd*, *J* = 9.0, 16.2, H–C(2)); 2.59 (*dd*, *J* = 4.1, 16.2, H'–C(2)); 3.24–3.33 (*m*, H–C(3)); 3.38, 3.39 (2*s*, $(MeO)_2C(4)$); 3.66 (*s*, CO_2Me); 4.12 (*d*, *J* = 5.6, H–C(4)). ^{13}C-NMR ($CDCl_3$, 75 MHz): 37.16 (*t*, C(2)); 49.92 (*d*, C(3)); 51.61 (*q*, CO_2Me); 54.95, 55.25 (2*q*, $(MeO)_2C(4)$); 107.15 (*d*, C(4)); 172.66 (*s*, C(1)). EI-MS: 178 (< 1, $[M+H]^+$), 160 (< 1, $[M-NH_3]^+$), 146 (10, $[M-MeO]^+$), 129 (1, $[M-NH_3-MeO]^+$), 114 (9, $[M-MeO-MeOH]^+$), 102 (31, $[M-(MeO)_2CH]^+$), 86 (14), 75 (100, $(MeO)_2CH^+$), 70 (14), 60 (8), 47 (9), 43 (9), 28 (4). HR-ESI-MS: 386.1794 (30), 364.1983 (25), 334.1874 (25), 307.1877 (74), 288.1428 (25), 200.0899 (100, $[M+Na]^+$, $C_7H_{15}NNaO_4^+$; calc. 200.0899). Anal. calc. for $C_7H_{15}NO_4$ (177.20): C 47.45, H 8.53, N 7.90; found: C 47.62, H 8.45, N 7.89.

*Methyl (5*R*,6*R*,7*S*,8*S*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-2-acetate* (**27**) *and Methyl (5*R*,6*R*,7*S*,8*R*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-2-acetate* (**28**). *a*) A suspension of **26** (25 mg, 45.1 μmol) and $HgCl_2$ (17 mg, 62.6 μmol) in THF (0.5 ml) was treated with **25** (48 mg, 0.271 mmol), stirred for 18 h at 22°, diluted with AcOEt (5 ml), and filtered over *Celite* (the solid was washed with 45 ml of AcOEt). The combined filtrate and washing was washed with brine (40 ml), dried ($MgSO_4$), filtered, and evaporated. A soln. of the residue (61 mg) in toluene (1.5 ml) was treated with $TsOH \cdot H_2O$ (40 mg, 0.210 mmol), stirred for 40 h at 60°, cooled to 22°, diluted with Et_2O (50 ml), and washed with sat. $NaHCO_3$ soln. (3 × 25 ml). The combined aq. layers were extracted with Et_2O (2 × 30 ml). The combined org. layers were washed with H_2O (50 ml) and brine (50 ml), dried ($MgSO_4$), filtered, and evaporated. FC (hexane/AcOEt 3:1 → 2:1) gave **27** (9.1 mg, 32%), **27**/**28** 22:78 (1.2 mg, 4%) and **28** (5.9 mg, 21%).

b) A suspension of **26** (25 mg, 45.1 μmol), $HgCl_2$ (23 mg, 84.7 μmol), and Et_3N (10 μl, 71.7 μmol) in THF (0.5 ml) was treated with **25** (48 mg, 0.271 mmol), and stirred for 4 h at 22°. Workup, treatment of the residue (54 mg) with $TsOH \cdot H_2O$, and FC (as described in *a*) gave **27** (7.8 mg, 27%), **27**/**28** 68:32 (1.0 mg, 4%) and **28** (6.1 mg, 21%).

c) A suspension of **26** (25 mg, 45.1 μmol) and HgO (18 mg, 83.1 μmol) in THF (0.5 ml) was treated with **25** (48 mg, 0.271 mmol), and stirred for 96 h at 22°. Workup, treatment of the residue (48 mg) with $TsOH \cdot H_2O$, and FC (as described in *a*) gave **27** (3.5 mg, 12%), **27**/**28** 74:26 (5.5 mg, 19%) and **28** (2.2 mg, 8%).

d) A suspension of **26** (25 mg, 45.1 μmol) and $Hg(OAc)_2$ (19 mg, 59.6 μmol) in THF (0.5 ml) was treated with **25** (48 mg, 0.271 mmol), and stirred for 2 h at 22°. Workup, treatment of the residue (52 mg) with $TsOH \cdot H_2O$, and FC (as described in *a*) gave **27** (6.7 mg, 23%), **27**/**28** 50:50 (1.4 mg, 5%) and **28** (5.1 mg, 18%).

e) A suspension of **26** (25 mg, 45.1 μmol) and $HgBr_2$ (21 mg, 58.3 μmol) in THF (0.5 ml) was treated with **25** (48 mg, 0.271 mmol), and stirred for 24 h at 22°. Workup, treatment of the residue (29 mg) with $TsOH \cdot H_2O$, and FC (as described in *a*) gave **27** (2.4 mg, 8%), **27**/**28** 55:45 (1.7 mg, 6%) and **28** (2.3 mg, 8%).

f) A suspension of **26** (25 mg, 45.1 μmol) and $Hg(OTf)_2$ (30 mg, 60.2 μmol) in THF (0.5 ml) was treated with **25** (48 mg, 0.271 mmol), and stirred for 24 h at 22°. Workup, treatment of the residue (37 mg) with $TsOH \cdot H_2O$, and FC (as described in *a*) gave **27** (3.7 mg, 13%), **27**/**28** 50:50 (0.3 mg, 1%) and **28** (4.6 mg, 16%).

g) The experiment described in *a* was repeated on a large scale: a suspension of **26** (235 mg, 0.424 mmol) and $HgCl_2$ (160 mg, 0.589 mmol) in THF (5 ml) was treated with **25** (458 mg, 2.58 mmol), and stirred for 18 h at 22°. Workup, treatment of the residue (461 mg) with $TsOH \cdot H_2O$ (370 mg, 1.95 mmol) in toluene (10 ml), and FC (as described in *a*) gave **27** (118 mg, 44%), **27**/**28** 50:50 (5 mg, 2%) and **28** (94 mg, 35%).

Data of **27**: R_f (hexane/AcOEt 1:1) 0.58. $[\alpha]_D^{25} = +48.1$ (*c* = 1.00, $CHCl_3$). UV ($CHCl_3$): 285 (2.37), 264 (2.90), 258 (2.96), 240 (3.51). IR ($CHCl_3$): 3090*w*, 3067*w*, 3032*m*, 3012*m*, 2955*m*, 2870*m*, 1952*w*, 1876*w*, 1814*w*, 1737*s*, 1633*w*, 1605*w*, 1562*w*, 1497*m*, 1455*m*, 1438*m*, 1362*m*, 1267*m*, 1152*s*, 1096*s*, 1028*s*, 910*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): see *Table 4*; additionally, 3.71 (br. *s*, CH_2–C(2)); 3.73 (*s*, MeO); 3.77 (irrad. at 4.18 → *d*, *J* = 10.3); 3.87 (irrad. at 3.77 → change, irrad. at 4.18 → change); 3.88 (irrad. at 4.11 → change, irrad. at 4.18 → change); 4.11 (irrad. at 4.75 → *d*, *J* = 7.5); 4.18 (irrad. at 3.77 → *dd*, *J* ≈ 2.2, 7.5); 4.46 (*d*, *J* = 11.8, PhC*H*); 4.48 (*d*, *J* = 11.2, PhC*H*); 4.51 (*d*, *J* = 11.5, PhC*H*); 4.70 (*d*, *J* = 11.2, PhC*H*); 4.75 (irrad. at 4.11 → *s*); 4.827 (*d*, *J* = 11.2, PhC*H*); 4.833 (*d*, *J* = 11.8, PhC*H*); 4.84 (*d*, *J* = 11.2, PhC*H*); 5.15 (*d*, *J* = 11.5, PhC*H*); 7.19–7.22 (*m*, 2 arom. H);

Table 4. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Protected and Deprotected* gluco-*Imidazoles* **14**–**17**, **27**, *and* **30**

	14		**15**	**16**	**17**	**27**	**30**
Solvent	CD_3OD	D_2O	D_2O	CD_3OD	D_2O	$CDCl_3$	$CDCl_3$
H–C(3)	8.06	8.01	7.53	7.22	7.03	7.03	7.76
H–C(5)	3.98–4.04	4.07–4.12	3.86–3.98	3.84–3.94	3.95–3.99	4.18	4.27
H–C(6)	3.85	3.96	3.79	3.83	3.91	3.88	3.83
H–C(7)	3.78	3.83	3.65	3.67	3.75	4.11	4.16
H–C(8)	4.58	4.64	4.49	4.55	4.56	4.75	4.80
CH–C(5)	3.96	4.09	3.86–3.98	3.93	4.02	3.77	3.77
CH′–C(5)	4.20	4.26	4.10	4.15	4.19	3.87	3.87
J(5,6)	7.8	8.4	9.7	8.4	9.0	7.8	7.8
J(6,7)	9.3	10.0	8.7	8.4	9.0	7.5	5.9
J(7,8)	7.8	9.0	7.5	8.4	8.4	5.3	4.1
J(5,CH)	4.4	3.5	[a])	3.7	2.8	5.3	5.6
J(5,CH′)	2.2	3.4	2.8	1.9	2.8	2.8	2.8
J(CH,CH′)	11.5	13.4	14.0	11.8	12.2	10.3	10.6

[a]) Not assigned.

Table 5. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the Protected and Deprotected* gluco-*Imidazoles* **14**–**17**, **27**, *and* **30**, *and of the Protected and Deprotected* manno-*Imidazoles* **20**, **21**, *and* **28**

	Solvent	C(2)	C(3)	C(5)	CH_2–C(5)	C(6)	C(7)	C(8)	C(8a)
gluco									
14	CD_3OD	133.04	125.71	63.44	61.13	69.64[a])	75.78	68.89[a])	149.60
15	D_2O	137.30	121.37	60.96	58.66	67.17[a])	74.40	67.83[a])	146.61
16	CD_3OD	134.97	117.08	62.88	61.18	69.85[a])	76.26	69.16[a])	147.59
17	D_2O	137.58	114.69	60.12	58.52	67.93[a])	74.64	67.09[a])	145.38
27[b])	$CDCl_3$	134.70	115.28	57.89	68.09	75.92	81.83	74.04	143.04
30	$CDCl_3$	133.04	124.16	58.05	67.67	76.27	81.00	72.82	144.54
manno									
20	CD_3OD	135.03	117.89	63.81	62.90	67.26	72.75	65.52	146.27
21	D_2O	132.71	117.01	62.10[a])	59.46	65.08	69.50	62.23[a])	143.10
28[b])	$CDCl_3$	134.70	117.18	59.73	70.58	73.92	80.09	68.59	142.26

[a]) Assignment may be interchanged. [b]) Assignments based on HSQC-GRASP spectrum.

7.27–7.45 (*m*, 18 arom. H). ^{13}C-NMR ($CDCl_3$, 75 MHz): see *Table 5*; additionally, 34.57 (*t*, CH_2–C(2)); 51.87 (*q*, MeO); 72.33, 73.14, 73.77, 74.02 (4*t*, 4 PhCH_2); 127.32–128.31 (several *d*); 137.15, 137.40, 137.62, 138.08 (4*s*); 171.48 (*s*, C=O). HR-MALDI-MS: 655.2783 (58, $[M+Na]^+$, $C_{39}H_{40}N_2NaO_6^+$; calc. 655.2784), 633.2964 (89, $[M+H]^+$, $C_{39}H_{41}N_2O_6^+$; calc. 633.2965), 525.2431 (100, $[M-BnO]^+$, $C_{32}H_{33}N_2O_5^+$; calc. 525.2389).

Data of **28**: R_f (hexane/AcOEt 1:1) 0.43. $[\alpha]_D^{25} = -29.8$ ($c = 0.99$, $CHCl_3$). UV ($CHCl_3$): 301 (2.34), 264 (2.92), 259 (2.96), 240 (3.49). IR ($CHCl_3$): 3090*w*, 3067*w*, 3032*m*, 3012*m*, 2955*m*, 2870*m*, 1952*w*, 1875*w*, 1810*w*, 1738*s*, 1608*w*, 1585*w*, 1563*w*, 1497*m*, 1455*m*, 1438*m*, 1407*w*, 1364*m*, 1267*m*, 1101*s*, 1027*s*, 910*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): see *Table 6*; additionally, 3.63 (irrad. at 4.11 → *d*, *J* = 10.3); 3.66 (br. *s*, CH_2–C(2)); 3.72 (*s*, MeO); 3.76 (irrad. at 4.11 → *d*, *J* = 10.0); 3.90 (irrad. at 4.32 → *d*, *J* = 2.8, irrad. at 4.80 → *d*, *J* = 9.3); 4.11 (irrad. at 3.76 → *dd*, *J* = 5.3, 7.2); 4.32 (irrad. at 3.90 → *d*, *J* = 7.2); 4.45 (*d*, *J* = 12.5, PhC*H*); 4.49 (*d*, *J* = 12.8, PhC*H*); 4.62 (*d*, *J* = 11.2, PhC*H*); 4.64 (*d*, *J* = 11.8, PhC*H*); 4.68 (*d*, *J* = 10.9, PhC*H*); 4.71 (*d*, *J* = 11.8, PhC*H*); 4.76 (*d*, *J* = 12.1, PhC*H*); 4.80 (irrad. at 3.90 → *s*); 5.02 (*d*, *J* = 10.9, PhC*H*); 7.25–7.41 (*m*, 20 arom. H). ^{13}C-NMR ($CDCl_3$, 75 MHz): see *Table 5*; additionally, 34.62 (*t*, CH_2–C(2)); 51.93 (*q*, MeO); 70.51, 71.65, 73.04, 74.82 (4*t*, 4 PhCH_2); 127.23–128.28 (several *d*); 137.34, 137.66, 137.83, 138.06 (4*s*); 171.39 (*s*, C=O). HR-MALDI-MS:

Table 6. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Protected and Deprotected* manno-*Imidazoles* **20**, **21**, *and* **28**

	20	**21**	**28**
Solvent	CD_3OD	D_2O	$CDCl_3$
H–C(3)	7.26	7.38	7.13
H–C(5)	3.86–3.93	4.18	4.11
H–C(6)	4.12	4.34	4.32
H–C(7)	3.83	4.12	3.90
H–C(8)	4.82	5.13	4.80
CH–C(5)	3.89	4.10	3.63
CH'–C(5)	4.08–4.18	4.25	3.76
J(5,6)	7.5	6.9	6.8
J(6,7)	8.7	9.0	9.3
J(7,8)	3.7	3.4	3.1
J(5,CH)	5.6	3.7	6.8
J(5,CH′)	[a])	2.8	3.1
J(CH,CH′)	13.7	12.5	10.3

[a]) Not assigned.

655.2784 (42, $[M+Na]^+$, $C_{39}H_{40}N_2NaO_6^+$; calc. 655.2784), 633.2965 (100, $[M+H]^+$, $C_{39}H_{41}N_2O_6^+$; calc. 633.2965), 525.2404 (71, $[M-BnO]^+$, $C_{32}H_{33}N_2O_5^+$; calc. 525.2389). Anal. calc. for $C_{39}H_{40}N_2O_6$ (632.75): C 74.03, H 6.37, N 4.43; found: C 73.99, H 6.41, N 4.57.

*Methyl (5*R*,6*R*,7*S*,8*S*)-5,6,7,8-Tetrahydro-6,7,8-trihydroxy-5-(hydroxymethyl)imidazo[1,2-*a*]pyridine-2-acetate* (**16**). A soln. of **27** (110 mg, 0.174 mmol) in AcOEt/MeOH/AcOH 1:1:1 (2.4 ml) was treated with 10% Pd/C (75 mg), hydrogenated at 6 bar and 22° for 40 h, and filtered over *Celite* (washing with 30 ml of MeOH/H_2O 9:1). Evaporation of the combined filtrate, washing, and FC (AcOEt/MeOH/H_2O 20:1:1 → 10:1:1 → 7:1:1) gave crude **16** (50 mg) as a brownish solid. A soln. of crude **16** in MeOH (3 ml) was treated with activated charcoal and stirred for 20 min. Filtration, evaporation, and lyophilisation yielded **16** (43.2 mg, 91%). White solid. R_f (AcOEt/MeOH/H_2O 7:1:1) 0.11. $[\alpha]_D^{25} = -20.6$ ($c = 1.02$, MeOH). pK_{HA} = 5.03. UV (MeOH): 221 (3.63). IR (0.6% in KBr): 3600–2400*s* (br.), 2955*m*, 2902*m*, 1716*s*, 1638*m*, 1571*w*, 1440*m*, 1407*m*, 1359*m*, 1312*m*, 1226*m*, 1183*m*, 1105*m*, 1066*m*, 1024*m*, 940*w*, 906*w*, 870*w*. ^{1}H-NMR (CD_3OD, 300 MHz): see *Table 4*; additionally, 3.66 (br. *s*, CH_2–C(2)); 3.67 (irrad. at 3.83 → change, irrad. at 4.45 → *d*, $J \approx 8.4$); 3.73 (*s*, MeO); 3.83 (irrad. at 3.67 → *d*, $J \approx 8.7$); 3.84–3.94 (irrad. at 4.15 → change); 3.93 (irrad. at 4.15 → *d*, $J \approx 3.4$); 4.15 (irrad. at 3.93 → *d*, $J \approx 2.0$); 4.55 (irrad. at 3.67 → *s*). ^{13}C-NMR (CD_3OD, 75 MHz): see *Table 5*; additionally, 33.67 (*t*, *C*H_2–C(2)); 52.98 (*q*, MeO); 174.19 (*s*, C=O). HR-MALDI-MS: 295.0898 (89, $[M+Na]^+$, $C_{11}H_{16}N_2NaO_6^+$; calc. 295.0906); 273.1078 (100, $[M+H]^+$, $C_{11}H_{17}N_2O_6^+$; calc. 273.1086); 255.0967 (6, $[M-OH]^+$, $C_{11}H_{15}N_2O_5^+$; calc. 255.0981).

*(5*R*,6*R*,7*S*,8*S*)-5,6,7,8-Tetrahydro-6,7,8-trihydroxy-5-(hydroxymethyl)imidazo[1,2-*a*]pyridine-2-acetic Acid* (**17**). A soln. of **16** (20 mg, 73.5 μmol) in 0.4M soln. of KOH in EtOH/H_2O 4:1 (1 ml) was heated at 50° for 1 h and evaporated. The residue was taken up in H_2O (3 ml) and applied to ion-exchange chromatography (*Amberlite CG-120*, H^+ form, elution with 0.1M aq. NH_3). Evaporation and lyophilisation gave **17** (16.3 mg, 86%). Colourless hygroscopic resin. R_f (AcOEt/MeOH/H_2O 3:1:1) 0.09. $[\alpha]_D^{25} = -27.8$ ($c = 0.76$, H_2O). pK_{HA} = 6.40 (no additional p*K* value was observed in the pH range 2.9–7.9). UV (H_2O): 224 (3.62). IR (0.3% in KBr): 3600–2400*s* (br.), 2953*m*, 2920*m*, 2852*w*, 1575*s*, 1506*m*, 1459*m*, 1390*s*, 1327*m*, 1273*m*, 1197*w*, 1178*w*, 1106*m*, 1070*m*, 1019*m*, 904*w*, 873*w*, 737*m*. ^{1}H-NMR (D_2O, 300 MHz): see *Table 4*; additionally, 3.43 (br. *s*, CH_2–C(2)). ^{13}C-NMR (D_2O, 75 MHz): see *Table 5*; additionally, 36.56 (*t*, *C*H_2–C(2)); 179.47 (*s*, C=O). HR-MALDI-MS: 281.0743 (45, $[M+Na]^+$, $C_{10}H_{14}N_2NaO_6^+$; calc. 281.0750), 259.0927 (100, $[M+H]^+$, $C_{10}H_{15}N_2O_6^+$; calc. 259.0930), 227.0656 (30, $[M-CH_2OH]^+$, $C_9H_{11}N_2O_5^+$; calc. 227.0668).

*Methyl (5*R*,6*R*,7*S*,8*R*)-5,6,7,8-Tetrahydro-6,7,8-trihydroxy-5-(hydroxymethyl)imidazo[1,2-*a*]pyridine-2-acetate* (**20**). A soln. of **28** (90 mg, 0.142 mmol) in AcOEt/MeOH/AcOH 1:1:1 (2.1 ml) was treated with 10% Pd/C (60 mg), hydrogenated at 6 bar and 22° for 40 h, and filtered over *Celite* (washing with 30 ml of MeOH/H_2O 9:1). Evaporation of the combined filtrate, washing, FC (AcOEt/MeOH/H_2O 1:0:0 → 15:1:1 →

7:1:1), and lyophilisation gave **20** (33.5 mg, 87%). White solid. R_f (AcOEt/MeOH/H_2O 7:1:1) 0.13. $[\alpha]_D^{25} = -19.0$ ($c = 1.01$, MeOH). p$K_{HA} = 4.61$. UV (MeOH): 221 (3.67). IR (0.3% in KBr): 3600–2400*s* (br.), 2954*m*, 2924*m*, 2852*w*, 1731*s*, 1636*w*, 1568*w*, 1510*w*, 1457*m*, 1439*m*, 1407*m*, 1354*m*, 1263*m*, 1215*m*, 1177*m*, 1092*m*, 1063*m*, 1019*m*, 902*w*, 834*w*. ^{1}H-NMR (CD_3OD, 300 MHz): see *Table 6*; additionally, 3.61 (br. *s*, CH_2–C(2)); 3.69 (*s*, MeO); 3.83 (irrad. at 4.12 → *d*, $J \approx 3.4$, irrad. at 4.82 → *d*, $J = 8.7$); 3.86–3.93 (irrad. at 4.12 → change); 4.12 (irrad. at 3.83 → *d*, $J \approx 6.8$); 4.82 (irrad. at 3.83 → *s*). ^{13}C-NMR (CD_3OD, 75 MHz): see *Table 5*; additionally, 34.14 (*t*, *C*H_2–C(2)); 52.58 (*q*, MeO); 173.13 (*s*, C=O). HR-MALDI-MS: 295.0899 (100, $[M+Na]^+$, $C_{11}H_{16}N_2NaO_6^+$; calc. 295.0906); 273.1086 (94, $[M+H]^+$, $C_{11}H_{17}N_2O_6^+$; calc. 273.1086).

*(5*R*,6*R*,7*S*,8*R*)-5,6,7,8-Tetrahydro-6,7,8-trihydroxy-5-(hydroxymethyl)imidazo[1,2-*a*]pyridine-2-acetic Acid* (**21**). A soln. of **20** (15 mg, 55.1 μmol) in 0.4M soln. of KOH in EtOH/H_2O 4:1 (1 ml) was heated at 50° for 1 h, evaporated. The residue was taken up in H_2O (3 ml) and applied to ion-exchange chromatography (*Amberlite CG-120*, H^+ form, elution with 0.1M aq. NH_3). Evaporation and lyophilisation gave **21** (11.5 mg, 81%) as a colourless hygroscopic resin containing substantial amounts of H_2O. The sample for microanalysis was dried for 8 d at 10^{-4} Torr. R_f (AcOEt/MeOH/H_2O 3:1:1) 0.07. $[\alpha]_D^{25} = -20.2$ ($c = 0.52$, H_2O). p$K_{HA} = 5.08$ (no additional p*K* value was observed in the pH range 2.6–5.4). UV (H_2O): 225 (3.76). IR (0.4% in KBr): 3600–2400*s* (br.), 2918*m*, 1583*s*, 1458*m*, 1385*s*, 1271*m*, 1168*m*, 1096*m*, 1069*s*, 1015*m*, 903*m*, 827*w*, 757*m*. ^{1}H-NMR (D_2O, 300 MHz): see *Table 6*; additionally, 3.62 (br. *s*, CH_2–C(2)). ^{13}C-NMR (D_2O, 75 MHz): see *Table 5*; additionally, 34.05 (*t*, *C*H_2–C(2)); 176.77 (*s*, C=O). HR-MALDI-MS: 281.0743 (57, $[M+Na]^+$, $C_{10}H_{14}N_2NaO_6^+$; calc. 281.0750), 259.0926 (100, $[M+H]^+$, $C_{10}H_{15}N_2O_6^+$; calc. 259.0930). Anal. calc. for $C_{10}H_{14}N_2O_6 \cdot H_2O$ (276.24): C 43.48, H 5.84, N 10.14; found: C 43.16, H 5.60, N 10.20.

*Methyl (5*R*,6*R*,7*S*,8*S*)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-2-carboxylate* (**30**). A suspension of **29** (144 mg, 0.245 mmol), MnO_2 (550 mg, 6.33 mmol, *Aldrich 21,764–6*) and NaCN (70 mg, 1.43 mmol) in MeOH (8 ml) was treated with AcOH (40 μl, 0.699 mmol), stirred at 22° for 3 h, and filtered through *Celite* (washing with 20 ml of MeOH and 20 ml of AcOEt). After evaporation, a soln. of the residue in AcOEt (30 ml) was washed with H_2O (20 ml) and brine (20 ml), dried (Na_2SO_4), filtered, and evaporated. FC (hexane/AcOEt 2:1 → 1:1) gave **29** (8.8 mg, 6%) and **30** (116 mg, 77%).

Data of **29**: see [12].

Data of **30**: Colourless oil. R_f (hexane/AcOEt 1:1) 0.31. $[\alpha]_D^{25} = +40.0$ ($c = 1.03$, $CHCl_3$). UV ($CHCl_3$): 244 (4.00). IR ($CHCl_3$): 3159*w*, 3090*w*, 3067*w*, 3031*m*, 3012*m*, 2952*m*, 2914*w*, 2869*m*, 1952*w*, 1876*w*, 1810*w*, 1716*s*, 1602*w*, 1585*w*, 1549*m*, 1497*w*, 1454*m*, 1424*w*, 1361*m*, 1329*m*, 1250*m*, 1167*m*, 1096*s*, 1069*s*, 1028*m*, 1011*m*, 942*w*, 910*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): see *Table 4*; additionally, 3.77 (irrad. at 4.27 → *d*, $J = 10.3$); 3.83 (irrad. at 4.16 → *d*, $J \approx 6.5$, irrad. at 4.27 → *d*, $J \approx 5.6$); 3.87 (irrad. at 4.27 → *d*, $J = 10.6$); 3.92 (*s*, MeO); 4.16 (irrad. at 3.83 → *d*, $J = 4.4$); 4.456 (*d*, $J = 11.2$, PhC*H*); 4.459 (*d*, $J = 12.8$, PhC*H*); 4.51 (*d*, $J = 12.1$, PhC*H*); 4.59 (*d*, $J = 11.5$, PhC*H*); 4.74 (*d*, $J \approx 11.2$, PhC*H*); 4.75 (*d*, $J = 11.5$, PhC*H*); 4.78 (*d*, $J = 11.5$, PhC*H*); 4.80 (irrad. at 4.16 → *s*); 5.02 (*d*, $J = 11.5$, PhC*H*); 7.14–7.20 (*m*, 2 arom. H); 7.24–7.40 (*m*, 18 arom. H). ^{13}C-NMR ($CDCl_3$, 75 MHz): see *Table 5*; additionally, 51.64 (*q*, MeO); 72.11, 73.14, 73.25, 73.47 (4*t*, 4 Ph*C*H_2); 127.44–128.39 (several *d*); 136.81, 137.13, 137.19, 137.69 (4*s*); 163.17 (*s*, C=O). HR-MALDI-MS: 641.2629 (100, $[M+Na]^+$, $C_{38}H_{38}N_2NaO_6^+$; calc. 641.2627), 619.2818 (73, $[M+H]^+$, $C_{38}H_{39}N_2O_6^+$; calc. 619.2808), 511.2213 (52, $[M-BnO]^+$, $C_{31}H_{31}N_2O_5^+$; calc. 511.2233), 479.1958 (22, $[M-BnO-MeOH]^+$, $C_{30}H_{27}N_2O_4^+$; calc. 479.1971). Anal. calc. for $C_{38}H_{38}N_2O_6$ (618.72): C 73.77, H 6.19, N 4.53; found: C 73.57, H 6.45, N 4.31.

*Methyl (5*R*,6*R*,7*S*,8*S*)-5,6,7,8-Tetrahydro-6,7,8-trihydroxy-5-(hydroxymethyl)imidazo[1,2-*a*]pyridine-2-carboxylate* (**14**). A soln. of **30** (98 mg, 0.158 mmol) in AcOEt/MeOH/AcOH 1:1:1 (2.4 ml) was treated with 10% Pd/C (100 mg), hydrogenated at 6 bar and 22° for 46 h, and filtered over *Celite* (washing with 20 ml of MeOH/H_2O 9:1). Evaporation of the combined filtrate and washing, co-evaporation with toluene (3 × 5 ml), and FC (AcOEt/MeOH/H_2O 1:0:0 → 10:1:1) gave crude **14** (43 mg) as a brownish solid. A soln. of crude **14** in MeOH (3 ml) was treated with activated charcoal and stirred for 10 min. Filtration and evaporation yielded **14** (39.0 mg, 95%). White solid. R_f (AcOEt/MeOH/H_2O 10:1:1) 0.15. $[\alpha]_D^{25} = -37.7$ ($c = 1.01$, MeOH). UV (MeOH): 239 (3.77), 202 (3.51). IR (0.5% in KBr): 3600–2400*s* (br.), 2949*w*, 2923*w*, 1693*m*, 1640*m*, 1561*w*, 1447*w*, 1373*w*, 1340*w*, 1233*m*, 1104*m*, 1066*w*, 1012*m*, 943*w*, 904*w*, 864*w*, 772*w*. ^{1}H-NMR (CD_3OD, 300 MHz): see *Table 4*; additionally, 3.78 (irrad. at 3.85 → change, irrad. at 4.58 → *d*, $J = 9.3$); 3.85 (irrad. at 3.78 → change); 3.91 (*s*, MeO); 3.96 (irrad. at 4.20 → change); 3.98–4.04 (irrad. at 3.85 → change, irrad. at 4.20 → *dd*, $J \approx 4.4$, 7.5); 4.58 (irrad. at 3.78 → *s*). ^{1}H-NMR (D_2O, 300 MHz): see *Table 4*; additionally, 3.83 (irrad. at 3.96 → change, irrad. at 4.64 → *d*, $J = 9.7$); 3.89 (*s*, MeO); 3.96 (irrad. at 3.83 → change); 4.07–4.12 (irrad. at 3.96 → change, irrad. at 4.26 → change); 4.09 (irrad. at 4.26 → change); 4.64 (irrad. at 3.83 → *s*). ^{13}C-NMR (CD_3OD, 75 MHz):

see *Table 5*; additionally, 52.89 (*q*, MeO); 166.05 (*s*, C=O). HR-MALDI-MS: 281.0744 (44, $[M+Na]^+$, $C_{10}H_{14}N_2NaO_6^+$; calc. 281.0750), 259.0926 (100, $[M+H]^+$, $C_{10}H_{15}N_2O_6^+$; calc. 259.0930).

*(5*R*,6*R*,7*S*,8*S*)-5,6,7,8-Tetrahydro-6,7,8-trihydroxy-5-(hydroxymethyl)imidazo[1,2-*a*]pyridine-2-carboxylic Acid* (**15**). A soln. of **14** (20 mg, 77.5 μmol) in 0.4M soln. of KOH in EtOH/H_2O 4:1 (1 ml) was kept at 50° for 210 min and evaporated. The residue was taken up in H_2O (3 ml) and applied to ion-exchange chromatography (*Amberlite CG-120*, H^+ form, elution with 0.1M aq. NH_3). Evaporation and lyophilisation gave **15** (15.2 mg, 80%). Colourless hygroscopic resin. R_f (AcOEt/MeOH/H_2O 3:1:1) 0.08. $[\alpha]_D^{25} = -72.3$ ($c = 0.59$, H_2O). $pK_{HA} = 4.95$ (no additional p*K* value was observed in the pH range 2.2–5.5). UV (H_2O): 226 (3.94), 192 (4.02). IR (0.2% in KBr): 3600–2400*s* (br.), 2918*m*, 2852*m*, 1620*m*, 1574*s*, 1544*m*, 1401*s*, 1331*m*, 1269*m*, 1180*w*, 1106*m*, 1070*m*, 1029*m*, 908*w*, 869*w*, 782*m*. ^{1}H-NMR (D_2O, 300 MHz): see *Table 4*. ^{13}C-NMR (D_2O, 75 MHz): see *Table 5*; additionally, 169.46 (*s*, C=O). HR-MALDI-MS: 245.0768 (100, $[M+H]^+$, $C_9H_{13}N_2O_6^+$; calc. 245.0774), 290.0412 (31, $[M+2\ Na]^+$, $C_9H_{12}N_2Na_2O_6^+$; calc. 290.0491).

Inhibition Studies. Determination of the inhibition constants (K_i) or the IC_{50} values was performed with a range of inhibitor concentrations (typically 4–7 concentrations) that bracket the K_i or IC_{50} value, and substrate concentrations that bracket the K_M of each enzyme (for K_i, typically 5–7 concentrations), or correspond to it (for IC_{50}).

a) *Inhibition of* Caldocellum saccharolyticum *β-Glucosidase.* $K_M = 0.73–0.81$ mM. ([56]: $K_M = 0.51$ mM; [57]: $K_M = 0.51–0.78$ mM). Inhibition constants (K_i) and IC_{50} values were determined at 55° at an enzyme concentration of 0.005 units/ml, with a 0.08M KH_2PO_4/K_2HPO_4 buffer (pH 6.8) and 4-nitrophenyl β-D-glucopyranoside as the substrate. The enzymatic reaction was started after incubation of the enzyme (150 μl) in presence of the inhibitor (40 μl) during 1 h at 55° by the addition of the substrate (10 μl). The enzyme reaction was quenched by addition of 0.2M borate buffer (pH 9.0, 100 μl) after 30 min, and the absorption at 405 nm was taken as rate for the hydrolysis of the substrate after subtraction of the absorption of a blank probe (H_2O, buffer, substrate). IC_{50} Values were determined by plotting the reciprocal value of the rate of substrate hydrolysis *vs.* the inhibitor concentration. After fitting a straight line to the data by linear regression, the negative [*I*]-intercept of this plot provided the appropriate IC_{50} value. K_i Values were determined by taking the slopes from the *Lineweaver–Burk* plots [58] and plotting them *vs.* the inhibitor concentrations [59]. After fitting a straight line to the data by linear regression, the negative [*I*]-intercept of this plot provided the appropriate K_i value. α Values were determined by plotting the 1/*v* axis intercepts from the *Lineweaver–Burk* plots *vs.* the inhibitor concentrations [59]. After fitting a straight line to the data by linear regression, the negative [*I*]-intercept of this plot provided the appropriate $\alpha \cdot K_i$ value.

b) *Inhibition of Brewer's Yeast* α-*Glucosidase.* $K_M = 0.21$ mM. ([57]: $K_M = 0.18–0.25$ mM). Inhibition constants (K_i) and IC_{50} values were determined at 37° at an enzyme concentration of 0.13 units/ml, with a 0.08M KH_2PO_4/K_2HPO_4 buffer (pH 6.8) and 4-nitrophenyl α-D-glucopyranoside as the substrate. The enzymatic reaction was started after incubation of the enzyme (150 μl) in presence of the inhibitor (40 μl) during 1 h at 37° by the addition of the substrate (10 μl). The increase of absorption per min at 405 nm was taken as rate for the hydrolysis of the substrate. The increase was linear during 10 min. IC_{50} Values were determined by plots as described in *a*.

c) *Inhibition of Snail β-Mannosidase.* $K_M = 0.55–0.57$ mM ([14]: $K_M = 0.42–0.80$ mM). IC_{50} and K_i values were determined at 25° at an enzyme concentration of 0.048 units/ml, with a 0.04M acetate buffer (pH 4.5) and 4-nitrophenyl β-D-mannopyranoside as the substrate. The enzymatic reaction was started after incubation of the enzyme (100 μl) in presence of the inhibitor (50 μl) during 1 h at 25° by the addition of the substrate (50 μl). The enzyme reaction was quenched by addition of 0.2M borate buffer (pH 9.0, 100 μl) after 5 min, and the absorption at 405 nm was taken as rate for the hydrolysis of the substrate after subtraction of the absorption of a blank probe (H_2O, buffer, substrate). IC_{50}, K_i , and α values were determined by plots as described in *a*.

d) *Inhibition of* Jack *Beans* α-*Mannosidase.* $K_M = 2.11–2.13$ mM ([60]: $K_M = 2.5$ mM; [14]: $K_M = 1.8–2.8$ mM). As described in *c*, inhibition studies were carried out at 37° at an enzyme concentration of 0.086 units/ml, with a 0.04M acetate buffer (pH 4.5), containing 1.5 mmol of $ZnCl_2$ and 4-nitrophenyl α-D-mannopyranoside as the substrate. The enzymatic reaction was started after the incubation at 37° for 1 h.

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